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Health and Environmental Effects Profile for Carbofuran

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR CARBOFURAN

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16. ABSTRACT

The Health and Environmental Effects Profile for carbofurans was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for carbofurans.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
bw	Body weight
DNA	Deoxyribonucleic acid
GC	Gas chromatography
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOEL	Lowest observed-effect level
MATC	Maximum acceptable toxicant concentration
NOAEL	No observed-adverse-effect level
NOEL	No observed-effect level
ppb	Parts per billion
ppm	Parts per million
RNA	Ribonucleic acid
TLC	Thin layer chromatography
TLV	Threshold limit value
TWA	Time-weighted average

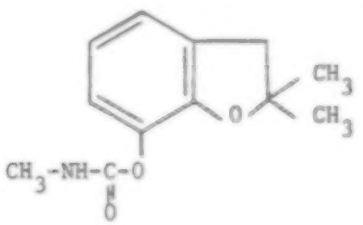
1. INTRODUCTION

Carbofuran is a synonym for 7-benzofuranol, 2,3-dihydro-2,2-dimethyl-, methylcarbamate. It is also known as carbamic acid, methyl-, 2,3-dihydro-2,2-dimethyl-7-benzofuranyl ester; carbamic acid, methyl-, 2,2-dimethyl-2,3-dihydro-benzofuran-7-yl ester (U.S. EPA/NIH, 1983); 2,3-dihydro-2,2-dimethyl-benzofuranyl-7-N-methyl-carbamate; 2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate; 2,2-dimethyl-2,3-dihydrobenzofuranyl-7-N-methylcarbamate (NIOSH, 1983); and 2,3-dihydro-2,2-dimethylbenzofuran-7-yl methylcarbamate (BCPC, 1977).

Carbofuran was introduced under the code number "FMC 10242" and trade name "Furadan" in 1967 by the Agricultural Chemical Division of the FMC Corporation (BCPC, 1977). Other trade names include Bay 70143, Curaterr, P1221, NIA 10242, Niagara 10242 and Yaltox (NIOSH, 1983).

1.1. STRUCTURE AND CAS NUMBER

The structure of carbofuran is given below (Ouellette and King, 1977):



Molecular formula: $C_{12}H_{15}NO_3$

Molecular weight: 221.3

The Chemical Abstracts Service (CAS) Registry number for carbofuran is 1563-66-2.

1.2. CHEMICAL AND PHYSICAL PROPERTIES

Carbofuran is a white, odorless, crystalline solid (BCPC, 1977) with the following characteristics:

Melting point:	150-152°C (Ouellette and King, 1977)
Vapor pressure:	2×10^{-5} mm Hg at 33°C (BCPC, 1977)
Density:	1.180 g/cm³ at 20°C (BCPC, 1977)
Solubility:	700 mg/l at 25°C (Ouellette and King, 1977)
K_{oc} (Soil sorption coefficient):	105 (measured) (Swann et al., 1980)
K_{ow} (Octanol/water partition coefficient):	2.07×10^{3} (Rao and Davidson, 1982)

Carbofuran is soluble to varying degrees in a number of organic solvents including acetone, acetonitrile and benzene, but it is essentially insoluble in agricultural formulation solvents (BCPC, 1977).

1.3. PRODUCTION DATA

Carbofuran is prepared by the thermal rearrangement and cyclization of 2-methylallyloxy-1-nitrobenzene to 2,3-dihydro-2,2-dimethyl-7-nitrobenzofuran, which is reduced to the amine, diazotized and converted to 2,3-dihydro-2,2-dimethylbenzofuran-7-ol which is then reacted with methyl isocyanate (BCPC, 1977).

Carbofuran is manufactured by the FMC Corp., Middleport, NY (SRI, 1983). The estimated production for 1972 was 6 million pounds. Domestic consumption was ~5 million pounds with the majority being used for agricultural purposes (von Rumker et al., 1974).

1.4. USE DATA

Carbofuran is the most effective insecticide currently available for use against corn rootworms and other soil pests. It is used extensively for alfalfa, peanuts, rice, sugar cane, tobacco, potatoes, sugar beets and sorghum (von Rumker et al., 1974).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. SOIL

The fate and transport of carbofuran in soil has been well characterized by numerous studies both in the field and in the laboratory. Ahmad et al. (1979a,b) reported that under laboratory conditions, the degradation of a granular formulation of carbofuran in four soils was very slow, with a half-life range of 60-75 days. Ou et al. (1982) reported the "mineralization rate" [rate of the complete recycling of an organic molecule to its mineral constituents, e.g., CO_2, H_2O (Atlas and Bartha, 1981)] of [ring-^{14}C] carbofuran in six soils to be much slower (half-life range of 216-944 days) than the "solvent extractable ^{14}C-activity disappearance rate" (half-life range of 5-261 days) at different temperatures and soil-water tensions. The difference was attributed to the formation of nonextractable ^{14}C-residues in soils (94.5% of the radioactivity was bound after 28 days of incubation). Solvent-extractable metabolites (<5% of applied ^{14}C) were identified as 3-hydroxycarbofuran, 3 ketocarbofuran, carbofuran phenol and 3-ketocarbofuranphenol. Rao and Davidson (1982) reviewed the literature and reported half-lives for solvent extractable carbofuran disappearance rates in soil as: 37 ± 35 days in laboratory studies; 44 ± 42 days for flooded soils; and 68 ± 42 days for soil in the field. The half-life for mineralization was 535 days.

The decomposition of carbofuran in soil depends upon a number of factors including pH, moisture content, aerobic and anaerobic conditions and history of prior carbofuran use. These factors have been found to affect both the hydrolysis and the microbial degradation of the insecticide.

Getzin (1973) found that the extent of hydrolysis of carbofuran in Sultan silt loam depended upon the pH of the soil. A 10-fold decrease was

noted in the half-life of ^{14}C-carbofuran hydrolysis at pH 7.8 ($t_{1/2}$ ~3 weeks), compared with soil at pH 4.3 ($t_{1/2}$ ~32 weeks). Aqueous alkaline hydrolysis (unspecified pH) of carbofuran was also observed to be rapid ($t_{1/2}$=8 days) at 25°C. Caro et al. (1973) noted that alkaline conditions resulted in a greater rate of carbofuran degradation in localized areas of watersheds treated with the insecticide. The half-life of carbofuran in a watershed with an overall pH of 6.35 was 94 days, whereas in the watershed at pH 5.2, the half-life was 117 days. A transformation product in soil was identified as 3-ketocarbofuran, which accumulated to 5-10% of the parent compound, and then disappeared at a similar rate. Also identified was the metabolite, 3-hydroxycarbofuran. Differences in degradation rates with pH were also noted by Venkateswarlu et al. (1977), who reported that 77% of the applied carbofuran persisted in an acid sulfate rice soil (pH remained 4.2 after 40 days of flooding), while in a similar soil, the pH of which rose to near neutrality during flooding, degradation was 65% complete in 40 days. Venkateswarlu et al. (1977) also found that more carbofuran phenol (hydrolysis product) was formed in flooded rice soil under anaerobic conditions. Carbofuran phenol disappeared and soil-bound residues increased when the system was agitated (aerobic conditions).

In experiments where ^{14}C-carbofuran and flooded soils were incubated under various combinations of alternating aerobic (shaking) and anaerobic (undisturbed) conditions, Venkateswarlu and Sethunathan (1979) postulated that the hydrolysis occurring under anaerobic conditions (Venkateswarlu et al., 1977) produced degradation products (i.e., carbofuran phenol) that served as substrates for microorganisms capable of further metabolizing the carbofuran skeleton under aerobic conditions.

Miles et al. (1981) found, under laboratory conditions, that after 8 weeks of incubation of carbofuran with soils, 77% remained in sterile muck while 25% remained in nonsterile muck; 50% remained in sterile loam, while none remained in nonsterile loam.

In a field study, Greenhalgh and Belanger (1981) applied carbofuran by broadcast to humic soil with organic matter content of 82% and observed a half-life of 15-38 days with the peak formation of 3-hydroxycarbofuran in 1-7 days and 3-ketocarbofuran in 16-36 days. Within 33 days, the number of soil bacteria including Actinomycetes was increased 4-fold. When the same field was retreated after 30 days, degradation was enhanced, indicating that the already induced active microorganisms required less time to proliferate.

Williams et al. (1976a) found that the rate of release of $^{14}CO_2$ after 2 weeks of incubating ^{14}[C=O]-carbofuran with vineyard soil was 40 times greater than when the soil had been autoclaved. After 8 weeks, 60% of the radioactivity was lost from nonsterile soil while the loss from sterile soil was negligible. They determined, on the basis of isolating eight microorganisms from the soil and incubating each in pure culture with carbofuran, that all eight were capable of degrading the insecticide to some extent, but three species of Actinomycetes were especially active. Carbofuran was rapidly lost from cornfield soils both with and without a history of insecticide use (<20% was recovered 20 days after application) (Felsot et al., 1981). No degradation was observed when the soils were autoclaved. Two species of bacteria isolated from the soil were active in degrading carbofuran in both pure culture and when added to sterile soil. Achromobacter sp. was less active than Pseudomonas sp., which degraded the insecticide by 99.5% in 30 days at 30°C. Kaufman et al. (1981) found that the evolution of $^{14}CO_2$ was more rapid from soil with a previous history of

carbofuran use than from soil that had not been previously treated when ^{14}[C=O]-carbofuran was applied. By use of various inhibitors, it was demonstrated that Actinomycetes or fungi or both were responsible for the degradation.

The transport of carbofuran in soil will depend upon its ability to volatilize, leach through soil or to be removed in runoff, all of which depend upon the extent of adsorption to soil. The relatively low value for the adsorption coefficient (K_{oc}) of 105 in three soils as measured by Swann et al. (1980) combined with its solubility of 700 mg/ℓ at 25°C suggests that carbofuran will be moderately to highly mobile in soil. Using 25 cm long water-saturated soil columns, McCall et al. (1980) found that carbofuran leached completely through three different soils.

Carbofuran may be lost from treated soils following heavy rains. Caro et al. (1973) found that runoff accounted for only 0.5 and 2.0% of the total carbofuran applied to two watersheds and that the residues were contained in the water rather than the sediment. Gorder et al. (1982) suggested that precipitation may be a major factor in the disappearance of carbofuran from treated fields, but they attributed the loss to the greater availability of carbofuran in moist soil to the processes of degradation and leaching, rather than to runoff. In laboratory experiments simulating rainfall, a greater degree of leaching was observed with more precipitation; however, in the field, low carbofuran residue levels were detected only to a depth of 7.5 cm. Because little leaching occurred in the field, and because a lag of ~5 days preceded rapid degradation in moist soil in laboratory studies, the major route of loss was thought to be via microbial degradation.

In a model agromicrocosm study, Koeppe and Lichtenstein (1982) found that a total of 49% of the applied ^{14}C-carbofuran was recovered in the

leachate from soil (500 g of a treated mixture of Plainfield sand and Plano silt loam on top of 500 g of untreated soil) and 37% was recovered from soils and corn following 3 weeks of incubation. The results indicated that carbofuran was susceptible to leaching. Sharom et al. (1980a) found that 95% of the carbofuran applied to Plainfield sand in a Buchner funnel was leached in the first 200 mℓ water rinse; the remainder was contained in the next leachate fraction. Even in soil with a high content of organic matter (75.3%), carbofuran was highly mobile; 75% of the applied amount was recovered in the first leachate fraction. Using soil TLC, Felsot and Wilson (1980) found that carbofuran was very mobile in seven different soil types with organic matter contents ranging from 0.4-16.8%. As discussed previously, Gorder et al. (1982) found that carbofuran readily leached through soil in a laboratory study, but in the field, carbofuran traveled only to a depth of 7.5 cm in soil (organic matter content of 3.1% and composed of 30% sand and 52% loam) after heavy rainfalls.

Limited information is available on the ability of carbofuran to volatilize from soil. Because the chemical has a reasonably low vapor pressure (2×10^{-5} mm Hg at 33°C) it is not expected to volatilize significantly from soils; however, some carbofuran volatilized from the foliage of rice plants following application of the insecticide to root tips or in the culture medium, but no volatilization was observed from the culture medium (Siddaramappa and Watanabe, 1979; Ferreira and Seiber, 1981). Ou et al. (1982) also speculated that the evaporation losses of carbofuran from soils, even at 35°C, would be insignificant. Thus, it appears that carbofuran undergoes hydrolysis under alkaline conditions in moist and flooded soils and is degraded microbially. Half-lives in soil are relatively long. Loss from soil by leaching was demonstrated in laboratory studies, but has not been confirmed in the field. Loss due to volatilization may not be significant.

2.2. WATER

The fate of carbofuran in aquatic media depends on its ability to hydrolyze, photodegrade and to biodegrade. The half-life of carbofuran added to natural water from a drainage canal or to distilled water (5 ppm carbofuran) was ~2 weeks, regardless of conditions (autoclaving, pH changes from 6.8-9.0, light or darkness), indicating that degradation occurred primarily by chemical processes (Sharom et al., 1980b). Seiber et al. (1978) reported that the half-life for carbofuran from rice paddy water and from rice paddy drainage ponds was 57 hours and was dependent upon pH ($t_{1/2}$=864 hours at pH 7; $t_{1/2}$=1.2 hours at pH 10). The rate of hydrolysis was also influenced to a lesser extent by sunlight and temperature.

Yu et al. (1974) found that carbofuran was rapidly hydrolyzed in a model aquatic ecosystem to which 5 mg ^{14}[C=O]-carbofuran was added. Radioactivity in the water declined rapidly, while trapped $^{14}CO_2$ rose steadily over 16 days. Identified hydrolysis products were parent carbofuran, 3-ketocarbofuran, N-hydroxymethylcarbofuran and 3-hydroxycarbofuran. Several unknown compounds were also formed. The hydrolysis of ^{14}C-ring-carbofuran resulted in carbofuranphenol, 3-ketocarbofuranphenol and 3-hydroxycarbofuranphenol as well as those named above for ^{14}[C=O]-carbofuran.

Seiber et al. (1978) mentioned that sunlight influenced the loss of carbofuran from water and drainage ponds from rice paddies. However, information pertaining to the rate of loss, amount of carbofuran degraded, and possible degradation products were not reported in the abstract. No other information on carbofuran photodegradation was available in the literature searched (see Appendix).

The degradation of carbofuran by aquatic microbes has been studied less than that by soil microorganisms. Vaishnav (1977) found that a mixture of pure cultured microorganisms were capable of co-metabolizing carbofuran in the presence of glucose. The metabolites were identified as 3-ketocarbofuran phenol, 3-ketocarbofuran and 3-hydroxycarbofuran. Since carbofuran is readily degraded by soil microbes, it is reasonable to assume that aquatic microbes also have this capability.

The transport of carbofuran in water will depend upon its ability to volatilize from water, sorb to sediment, accumulate in aquatic biota, and its water solubility.

The ability of carbofuran to volatilize from water was contraindicated by a study of carbofuran evaporation from the foliage of rice plants. No evaporation from the treated culture medium was observed in control experiments (Ferreira and Seiber, 1981).

The ability of carbofuran to sorb to components of the aquatic environment is important to transport mechanisms. Koeppe and Lichtenstein (1982) found that the aquatic component of an agromicrocosm contained only 0.3% of the applied ^{14}C-carbofuran after leaching through soil; 75% was bound as unextractable ^{14}C-labeled compounds in the bottom mud. Klaassen and Kadoum (1979) added carbofuran to ponds in concentrations of 0.025 ppm the first year and 0.050 ppm the second year. After the first treatment, residue levels of 10.6 ppb were found in surface water only and just on the first day. After the second treatment, residues in surface water amounted to 15 ppb while 26.4 and 46.2 ppb carbofuran residues were found in the shallow mud area and the deep mud area, respectively. Caro et al. (1973) found that runoff after rainfall from watersheds treated with carbofuran resulted in higher residue concentrations in the flume floor sediment (3.1 g

or 1.35 mg/kg) than in suspended solids (7.1 g or 0.83 mg/kg), although most of the carbofuran in runoff was dissolved in water (25 g or 0.103 mg/ℓ of runoff).

Residual levels of carbofuran from the irrigation water from rice fields treated with the pesticide averaged 0.327 mg/ℓ during 1973, 1974 and 1975 at the Texas Agricultural Experiment Station (Brown et al., 1979). The authors noted that these levels exceeded the 96-hour LC_{50} in the channel catfish and many other fish. Klaassen and Kadoum (1979) reported that carbofuran, applied to a pond at 0.025 mg/ℓ for 1 year followed by 0.050 mg/ℓ the second year, was detected in the water and sediment within 3 days following the 2-year treatment. No residual carbofuran was detected in zooplankton or fish samples collected from the pond. By 25 days after treatment, carbofuran was not detected (<0.004 mg/ℓ) in the water, sediment or aquatic organisms. Analysis for possible degradation products was not performed (Klaassen and Kadoum, 1979). Similarly, Brown et al. (1975) reported that carbofuran was rapidly removed from the water and occurred in sediments. Within 49 days, however, 75% of the applied carbofuran had disappeared from the water-sediment system and little was detectable as 3-hydroxy or 3-ketocarbofuran. Brown et al. (1975) additionally noted that these degradation products, 3-hydroxy- and 3-ketocarbofuran were more toxic than carbofuran in microbial toxicity tests.

Thus, because of the ready hydrolysis and the probable biodegradation of carbofuran, the insecticide probably does not persist in the aquatic environment. The portion that is carried while dissolved in water will hydrolyze, liberating CO_2 and other metabolites which may bind to bottom sediment. Carbofuran did not accumulate in aquatic organisms in a number of studies (see Section 6.4.) (Sanghu, 1971; Klassen and Kadoum, 1979; Yu et al., 1974).

2.3. AIR

Carbofuran can enter the atmosphere during spray drift application and through volatilization from foliage. As discussed previously, there is little likelihood that the compound will volatilize from water or soil.

Draper et al. (1981) monitored the air in and around fields during and 2 hours after aerial spraying of 0.5 lb active ingredient/acre of carbofuran to assess drift. The insecticide was detected in air samples collected at an adjacent site to the target field using glass fiber filters, indicating that carbofuran was present in the air in the particulate form. The concentration in air during the 17 minute sampling period was 0.7-3.3 $\mu g/m^3$ (TWA). When air samples were analyzed 2 hours later, the TWA concentration at the site had dropped to 0.1 $\mu g/m^3$. Some drift may have occurred, however carbofuran was not detected at any of the other sampling sites.

Siddaramappa and Watanabe (1979) demonstrated carbofuran loss by volatilization from the foliage of rice plants actively growing in culture medium containing ^{14}C-carbofuran. After 10 days, 5% of the initial radioactivity was trapped in ethylene glycol traps and TLC analysis revealed that the majority of radiolabel represented unchanged carbofuran. In similar experiments, Ferreira and Seiber (1981) found that carbofuran lost through volatilization from rice plants accounted for 5.8% of the initial residue in the plant. Thus, small amounts of carbofuran can enter the atmosphere through volatilization from the foliage.

The fate of carbofuran in the atmosphere will depend upon its reactions with O_3, NO_2 and free radicals (e.g., RO•, O• and RO_2•) and its ability to undergo photolysis. No data were available on the reactions of carbofuran with atmospheric molecules. The information on photolysis is

limited to the observation of Seiber et al. (1978) that sunlight influenced the rate of carbofuran loss from rice paddy water. Since carbofuran is relatively water soluble and readily hydrolyzed, vapors of carbofuran in the air may hydrolyze in high humidity or be precipitated by rainfall.

3. EXPOSURE

Only two soil monitoring studies were found. Williams et al. (1976b) found high residue levels of carbofuran, detected by GLC, in soils with known carbofuran use in Fraser Valley, British Columbia: in poorly drained clay muck, 0.78-1.18 ppm after the first year of application, 2.62 ppm after the second year; in well-drained clay muck, 0.78-2.08 ppm after the first year, 3.88 after the second year of application; in poorly drained clay, 0.38 ppm after the first year. Miles and Harris (1978) found carbofuran residues in 10 of 28 vegetable growing farm soils in Southern Ontario with a maximum level of 8.7 ppm carbofuran in one soil.

STORET contains monitoring data on carbofuran in water. There are 58 observations for carbofuran in water collected from 21 stations between 1979 and 1982. The mean concentration of carbofuran in water was 0.7 mg/ℓ and the maximum was <12.0 mg/ℓ. Of the 21 stations, 11 had undetectable levels (limits of detection not given).

Dudley and Karr (1980) failed to detect residues of carbofuran in the Black Creek Watershed, Allen County, Indiana, monitored in 1977-1978. The lower limit of detection by GC analysis was 0.1 ppm. Kadoum and Mock (1978) monitored water and sediment in tailwater pits collecting irrigation runoff in Haskell County, Kansas, in 1974. Carbofuran was detected in pit bottom sediment in 4 of 154 samples collected from 31 pits (4 pits implicated) at mean levels of 30.6-50.0 ppb (max. 759 ppb) and in tailwater in 15 of 154 samples collected from 31 pits (12 pits implicated) with mean levels of 24.1-35.2 ppb (max. 88.9 ppb). Woodham et al. (1975) found no carbofuran residues >0.01-0.05 ppm in pond sediments exposed to runoff from treated tobacco soil (number of samples not given in the abstract) monitored in North Carolina during 1971.

Gummer (1979) failed to detect carbofuran residues (limits of detection not given in the abstract) in surface water of prairies in Western Canada.

No information was found on monitoring for carbofuran in drinking water, edible crops or air.

4. PHARMACOKINETICS

4.1. ABSORPTION

The absorption of ^{14}C-carbofuran from the gastrointestinal tract of mice has been studied by Ahdaya et al. (1981). Female ICR mice (25-30 g, number not reported) were gavaged with [ring-^{14}C]-carbofuran in Emulphor: ethanol:water following a 12-hour fast at a dose of 1 mg/kg (1 μ Ci/mouse) and killed at various time intervals to determine the amount of radioactivity absorbed. The half-life of absorption was 10.0 minutes with 34.5, 44.7, 51.2, 63.4 and 67.4% of the administered radiolabel absorbed by 1, 5, 15, 30 and 60 minutes, respectively. Radioactivity appeared in the blood at a peak level of ~5% of the administered dose at 8 minutes. The absorption was further characterized in female ICR mice (25-30 g, number not reported) with stomachs surgically ligated at the pylorus 2 hours prior to intubation with the same dose given above (Ahdaya and Guthrie, 1982). At 15, 30 and 60 minutes after the administration of ^{14}C-carbofuran, 9.5, 15.1 and 18.8% of the administered dose, respectively, were absorbed by the ligated stomach. The gastrointestinal tracts of intact mice had absorbed 67.4% of the dose by this time (Ahdaya et al., 1981). The ratio of the dose absorbed by the ligated stomach to the dose absorbed by the intact gastrointestinal tract was 0.28, indicating that the majority of absorption occurred within the intestine (Ahdaya and Guthrie, 1982).

Shah et al. (1981) reported that the half-life for dermal penetration of ^{14}C-carbofuran (2.85 m Ci/mmol) applied to the skin of ICR female mice (25-30 g, number not reported) was 7.7 minutes with 28.5, 32.6, 71.7, 76.1 and 94.7% of the administered radioactivity absorbed by 1, 5, 15, 60 and 480 minutes, respectively.

Thus, carbofuran is readily absorbed by the gastrointestinal tract and through the skin of mice. Absorption studies of carbofuran in other species were not located in the literature searched.

4.2. DISTRIBUTION

The distribution of carbofuran in the tissues of mice administered the pesticide orally (Ahdaya et al., 1981) or dermally (Shah et al., 1981) or in rat tissues after oral administration (Dorough, 1968) has been determined.

Radioactivity appeared in the blood of female ICR mice (sample size not reported) given [ring-^{14}C]-carbofuran by gavage at a level of ~5% of the administered dose (1 mg/kg, 1 μ Ci) within 8 minutes (Ahdaya et al., 1981). By 20 minutes, the level had declined to 4% followed by a slight gradual increase after 40 minutes then gradual decline to 3% by 60 minutes. In the liver of these same animals, 10% of the administered radioactivity was detected within 7 minutes, followed by a decline to ~6% within 15 minutes. Peak intestinal levels of radiolabel reached 14% within 15 minutes and declined to 10% by 60 minutes. After the livers and intestines were removed from these mice, the radioactivity in the carcass was then determined. About 20% of the administered dose was detected in the carcass between 5 and 10 minutes and remained fairly constant throughout the 60-minute time course. Following absorption through the ligated stomachs of female ICR mice administered the same dosage as above, smaller percentages of absorbed radioactivity were detected in all tissues, reflecting the lower absorption rate (Ahdaya and Guthrie, 1982).

Distribution of radiolabel following dermal application of [ring-^{14}C] carbofuran (2.85 m Ci/mmol) in female ICR mice was reported by Shah et al. (1981). Plasma levels reached 1.7% of the absorbed dose in 15 minutes, with only 0.5% remaining in the blood at 60 minutes. Greater percentages were reached in the liver than in the blood with 2.4% recovered in 15 minutes.

Only 0.2% was found in fat after 15 minutes. In the carcass, 32.4, 67.3 and 66.4% of the absorbed dose was detected at 5, 15 and 60 minutes, respectively.

Dorough (1968) reported the following distribution of radioactivity, expressed as ppm equivalents, in rats (200 g, number and strain not reported) 8 hours after receiving an oral dose of 1 mg ^{14}C=O carbofuran/kg bw in Tween 20: blood, 0.30; brain, 0.09; bone, 0.06; kidney, 0.14; liver, 0.78; and leg muscle, 0.06. The report did not state specifically whether administration was via gavage or feeding.

4.3. METABOLISM

The metabolism of carbofuran has been studied in mice (Metcalf et al., 1968) and rats, both in vivo and in vitro (Dorough, 1968), and in bile duct cannulated rats (Marshall and Dorough, 1979).

Metcalf et al. (1968) administered [4,5,6-^{3}H]-carbofuran (1.68 m Ci/mmole) or N-$^{14}CH_3$-labeled carbofuran (0.104 m Ci/mmole) in propylene glycol by gavage to male Swiss white mice (sample size not reported). About 50% of the administered radiolabel from [4,5,6-^{3}H]-carbofuran or from N-$^{14}CH_3$-carbofuran was eliminated in urine collected after 24 hours. About 1.6% was expired as $^{14}CO_2$. The major urinary metabolites were identified as 3-hydroxycarbofuran, 3-ketocarbofuran and an appreciable amount of carbofuran phenol. Some minor metabolites were conjugated 3-ketocarbofuran and 3-ketocarbofuran phenol.

Oral administration of ^{14}C=O-carbofuran to rats (number and strain not specified) resulted in 45% of the administered dose (0.4 mg/kg, 2 m Ci/mmole) expired as $^{14}CO_2$ within 32 hours and 38% excreted in the urine (Dorough, 1968). When [ring-^{14}C]-carbofuran was administered (4 mg/kg; 0.07 m Ci/mmole), 92% of the radioactivity was excreted in the urine. The

urinary metabolites (excreted primarily as water-soluble conjugates) were 3-hydroxy-N-hydroxymethyl carbofuran, 3-hydroxycarbofuran, 3-hydroxycarbofuran phenol, 3-ketocarbofuran phenol, carbofuran phenol and several unknowns. In vitro incubation for 2 hours of ^{14}C=O-carbofuran with the 15,000 G supernatant from the rat liver homogenates resulted in 6.23% of the radioactivity as unknown metabolites, 1.76% as 3-hydroxy-N-hydroxymethyl-carbofuran, 6.4% as N-hydroxymethylcarbofuran, 21.1% as 3-hydroxycarbofuran, 0.28% as 3-ketocarbofuran and 60% as unchanged carbofuran.

Marshall and Dorough (1979) reported that the urinary metabolites of ^{14}C-carbofuran from bile-duct cannulated rats were composed of sulfate and glucuronide conjugates of 3-hydroxycarbofuran phenol, 3-ketocarbofuran phenol and carbofuran phenol, while 3-hydroxycarbofuran glucuronide was the major metabolite in bile.

4.4. ELIMINATION

Male Swiss mice receiving oral doses of ^{14}C-carbofuran or ^{3}H-carbofuran excreted ~50% of the administered radioactivity in the 24-hour urine. About 1.6% was expired as $^{14}CO_2$ when the radiolabel was on the N-$^{14}CH_3$ group (Metcalf et al., 1968).

Biphasic elimination of $^{14}CO_2$ from the lungs of rats administered ^{14}C carbofuran was reported by Hurst (1979) with 8-10 hours duration of the initial exponentially declining rate. Other details of this study (strain, sex, route of administration) were not available.

Within 120 hours after treating rats orally (method not given) with ^{14}C=O-carbofuran (0.4 mg/kg), 44.6% of the administered dose was expired as $^{14}CO_2$, 38.4% as urinary metabolite and 4.4% as fecal products. When ^{14}C-ring carbofuran (4.0 mg/kg) was given, 91.6% of the radioactivity was in the urine and 3.3% was in the feces at 120 hours. Urinary excretion was 79% complete by 24 hours and 86% complete by 48 hours (Dorough, 1968).

Male rats (350-400 g) with cannulated bile ducts excreted 28.5% of a single, orally administered dose of radiolabel from [ring-^{14}C]-carbofuran (0.1 mg/kg) in the bile within 2 days; urinary excretion accounted for 65.4%, while fecal excretion accounted for only 0.4% of the administered radiocarbon (Marshall and Dorough, 1979). When the excretion data for these cannulated rats are compared with the excretion data from intact rats as previously described (Dorough, 1968), it is apparent that enterohepatic cycling of biliary metabolites occurs in intact rats (i.e., biliary metabolites are reabsorbed from the intestine and ultimately excreted in the urine).

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of carbofuran were not encountered in the available literature. This compound is not scheduled for testing by the National Toxicology Progam (NTP, 1983). An abstract of a study by Lijinsky and Schmael (1978) indicates, however, that administration (route not specified) of nitrosocarbofuran induces tumors and carcinomas in rats. The authors suggested that reaction of carbofuran with nitrile within the environment or stomach may result in the formation of a carcinogenic nitroso compound.

5.2. MUTAGENICITY

The genotoxicity of carbofuran has been studied in a wide variety of testing systems including bacteria, yeast, corn, Drosophila melanogaster and in mouse, hamster and human cell cultures (Waters et al., 1982; Gentile et al., 1982; DeSaint-Georges-Gridelet et al., 1982; Wojciewchowski et al., 1982; Quarles et al., 1979). The results of these studies are summarized in Table 5-1. Negative or equivocal results were obtained in mutation assays using Salmonella typhimurium, Escherichia coli, Bacillus subtilis, Saccharomyces cerevisiae, Zea mays, Drosophila melanogaster, fetal hamster cells and human lung fibroblasts (Waters et al., 1982, Quarles et al., 1979; Gentile et al., 1982). A weak mutagenic response was observed in Chinese hamster V79 cells in the absence of activation but results were negative when irradiated Syrian hamster feeder cells were used for activation (Wojciechowski et al., 1982). A dose-related increase in the number of mouse erythroblasts with micronuclei was observed following oral treatment of mice with carbofuran (DeSaint-Georges-Gridelet et al., 1982). Details of these studies are given in Table 5-1.

TABLE 5-1

Mutagenicity Testing of Carbofuran

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100	plate incorporation	NR	+S9 +IS (Zea mays)* -S9 or IS*	- - -	NC	Gentile et al., 1982
Reverse mutation	S. typhimurium TA1535, TA1537 TA1538, TA98, TA100	plate incorporation	6 concentrations up to 10 mg/plate	±S9	-	A positive response was considered to be a dose-related increase in the number of revertants in at least 3 concentration levels.	Waters et al., 1982
Reverse mutation	Escherichia coli WP2	NR	6 concentrations up to 10 mg/plate	±S9	-	See above	Waters et al., 1982
Repair of primary DNA damage	E. coli P3748	spot test	NR	-S9	inconclusive	no growth inhibition was observed	Waters et al., 1982
Rec assay	Bacillus subtilis M45	spot test	NR	-S9	inconclusive	no growth inhibition was observed	Waters et al., 1982
Mitotic gene conversion	Saccharomyces cerevisiae D4	incubation with cell suspension	NR	±S9 +IS (Zea mays)* -S9 or IS*	- - -	NC	Gentile et al., 1982
Mitotic recombination	S. cerevisiae D3	NR	NR	±S9	- -	no recombinogenic activity with or without metabolic activation	Waters et al., 1982
Reverse mutation	Zea mays pollen	applied to soil before emergence of seedlings	2.24 eq. kg/ha	NA	-	NC	Gentile et al., 1982
Sex-linked recessive lethal	Drosophila melanogaster	exposure to male parent	NR	NA	-	failed to produce 0.2% increase in mutation rate over background	Waters et al., 1982
Micronucleus test	mouse erythroblasts	in vivo oral	5, 25, 75 or 150 mg/kg	NA	+	dose-related increase in polychromatic erythrocytes containing micronuclei at ≥5 mg/kg	DeSaint-Georges-Gridelet et al., 1982

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TABLE 5-1 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Comment	Reference
Resistance to ouabain	Chinese hamster V79 cells	cell culture	0.1, 0.5 or 1.0 mM	± irradiated Syrian hamster feeder cells	- +/-	- in the presence of activation; weakly mutagenic in the absence of activation	Wojciechowski et al., 1982
Colony transformation	hamster fetal cells	transplacental host-mediated	0.5 mg/kg i.p.	NA	-	0% of transformed colonies (0 transformed colonies/4876 colonies)	Quarles et al., 1979
Unscheduled DNA synthesis	human lung fibroblasts	cell culture	NR	±S9	-	no significant increase in ^{3}HTdR uptake	Waters et al., 1982

*IS = a lyphilized 1000 x 9 supernatant prepared from germinating Zea mays at the 3 leaf stage.

NA = Not applicable; NR = not reported; NC = no comment

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Although carbofuran was nonmutagenic in most of the assay systems cited, its nitrosated derivative was found to have mutagenic activity in the colony transformation assay in fetal hamster cells (Quarles et al., 1979), yielding upon plating at low density 45 transformed colonies in 7120 total colonies (0.6%). Positive results were obtained in the reverse mutation assay using S. typhimurium for nitrosocarbofuran at concentrations <2 mg/plate, and for the nitrosated metabolites of carbofuran, nitroso-3-ketocarbofuran (at 30 mg/plate) and nitroso-3-hydroxycarbofuran (at 120 mg/plate) (Nelson et al., 1980). Rickard (1980) also found nitrosocarbofuran to be mutagenic in the S. typhimurium reverse mutation assay. These studies suggest that nitroso derivatives of carbofuran or its metabolite, which may form in the environment or in vivo after ingestion, have the potential for genotoxicity.

5.3. TERATOGENICITY

McCarthy et al. (1971), in teratogenicity studies on beagle dogs, reported that carbofuran in the diet (≤50 ppm) produced no adverse effects on the health or reproductive behavior of the parents (males and females), and their offspring "appeared normal in every respect" (duration of exposure not reported). Teratogenicity studies with rats and rabbits also gave no evidence of teratogenic effects. These studies, performed for the FMC Corporation, were reported only in an abstract and no experimental details were included.

5.4. OTHER REPRODUCTIVE EFFECTS

Wolfe and Esher (1980) reported the absence of adverse reproductive and developmental effects attributable to carbofuran in male and female mice and their offspring housed together and fed diets containing 0 or 0.01% carbofuran for 8 months. The offspring born to groups of 7 male and 7 female Peromyscus gossypinus and 9 male and 9 female P. polionotus wild mice were

evaluated for a variety of developmental parameters up to age 21 days. No significant differences were observed between treated and control groups regarding litter size, body weight, appearance and behavior. Significantly decreased survival (44% mortality) in the treated parental animals was observed in P. polionotus ($p<0.01$) near the end of the study and, therefore, did not affect the reproductive data.

Shain et al. (1977) evaluated the effects of dietary carbofuran on ventral prostate homeostasis in male Sprague-Dawley rats. Twelve adult rats were given diets containing 30 ppm carbofuran for 90 days. Following treatment, blood samples were collected and the testes and ventral prostate of each rat were removed. Carbofuran was observed to decrease the number of available cytoplasmic androgen receptor sites and RNA content and increase the total androgen receptor sites in the ventral prostate, without affecting the size or cell content of the gland. Serum testosterone levels and testicular weights were not significantly affected by treatment.

Cambon et al. (1979) investigated the effect of several concentrations of carbofuran on the acetylcholinesterase activity in blood and various tissues of pregnant rats given a single gavage treatment. Groups of eight female Sprague-Dawley rats were fasted overnight and received either 0, 0.05, 0.25 or 2.5 mg carbofuran/kg bw by gavage on day 18 of gestation. The day on which sperm-positive vaginal smears were detected was considered day 1 of gestation. At 1, 5 and 24 hours after treatment, acetylcholinesterase activity was determined on the blood, liver and brain of the dams and fetuses. Eight of 32 rats given 2.5 mg/kg died within 30 minutes. Transient inhibition of acetylcholinesterase activity was observed at all dose levels; maternal and fetal blood acetylcholinesterase activity was significantly different from control levels in all dosage groups at 1 hour but not

24 hours after treatment. Other tissues with significant inhibition of acetylcholinesterase activity included the following: maternal liver 1 hour after 0.05 mg/kg dose, maternal brain and fetal liver 1 hour after a 0.25 mg/kg dose, maternal liver and fetal brain 5 hours after a 0.25 mg/kg dose, maternal and fetal brain and liver at 1 and 5 hours after a 2.5 mg/kg dose. The authors speculated that different results might have been obtained had the dams not been fasted overnight. Preliminary studies showed no carbamate-induced diminution of acetylcholinesterase activity in unfasted pregnant rats at a similar dose level. Further, Weil et al. (1973) reported more pronounced effects on reproduction in rats given carbamates by gavage than in rats given similar amounts in the diet.

Cambon et al. (1980) reported additional changes in maternal and fetal cerebral acetylcholinesterase levels following maternal oral exposure to carbofuran. Groups of 6 pregnant female Sprague-Dawley rats were given 2.5 mg carbofuran/kg by gavage on the 18th day of gestation. The day on which sperm-positive vaginal smears were observed was considered to be day 1 of gestation. The fetal and maternal brains were homogenized 90 minutes after dosing. The types and amounts of acetylcholinesterase isoenzymes were determined by gel electrophoresis. Significant inhibition of a cerebral acetylcholinesterase isoenzyme was observed in both dams and fetuses.

Barnett et al. (1980) examined the effect of maternal dietary carbofuran administration on the suppression of immunocompetence in offspring. Groups of 43, 23 and 18 mated F-3 dihybrid female mice were fed diets containing 0, 0.01 or 0.5 mg carbofuran/kg bw/day, respectively, from the day after vaginal plugs were observed until birth. Effects of carbofuran on offspring, gross appearance, body weight, serum immunoglobulin content and behavior were recorded. The offspring appeared overtly normal and no

effects on offspring mortality at age 28 days were observed. Transient disturbances of some serum immunoglobulins were observed in offspring of treated mice, but these disturbances did not appear to affect the incidence of disease or mortality.

Clegg (1979) reviewed several studies on the effects of pesticide administration on reproduction. The results from two unpublished three-generation reproduction studies of carbofuran were presented, but many experimental details were omitted. In one study reviewed by Clegg (1979), rats fed 100 ppm carbofuran in the diet (duration not given) had reduced weanling weight and survival and rats given 10 ppm carbofuran had questionable effects on mating index in the F_{2a} generation (McCarthy et al., 1971). In another study, the dietary administration of 30 ppm carbofuran was associated with reduced mating and lactation indices in the F_{2b} generation (species not specified) (Clegg, 1979). No further details were given.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Wolfe and Esher (1980) investigated the effects of subchronic dietary administration of diets containing 0 or 0.1% carbofuran in two species of wild mice. Groups of 7 male and 7 female P. gossypinus and 9 male and 9 female P. polionotis mice were maintained on the diet for 8 months. Control and treated groups did not differ significantly regarding food consumption, reproductive parameters and behavior. Offspring born to these mice were observed to have no adverse effects on development and behavior (see Section 5.4.). Mortality of 44% ($p<0.01$) was observed in treated P. polionotis. Deaths occurred primarily near the end of the study.

Male Sprague-Dawley rats (sample size not reported) fed 30 ppm carbofuran for 90 days had significantly ($p<0.01$) decreased body weight gain compared to controls (Shain et al., 1977). Food consumption in treated

groups was not different from control groups. Effects on ventral prostate homeostasis were observed (see Section 5.4.).

Rotaru et al. (1981) reported the absence of cumulative toxic effects in rats fed carbofuran diets for 180 days. Groups of 10 male adult Wistar rats were fed diets containing 0, 10 or 25 ppm carbofuran and underwent gross, enzymological and histopathological evaluation. Histopathological examinations were limited to the liver, kidneys, heart, lungs and spleen. No significant effects were observed on a variety of serum and hepatic enzymes with the exception of increases in lactic dehydrogenase (LDH) activity. Rats from the control, 10 ppm and 25 ppm groups had seric LDH activity of 0.87×10^{-2}, 1.42×10^{-2} and 1.23×10^{-2} mmoles substrate/minute/100 mℓ serum, respectively. When compared with controls, these increases were statistically significant in only the 10 ppm group ($p<0.01$ for 10 ppm). Liver homogenate from the control, 10 ppm and 25 ppm groups had LDH activities of 29.4, 37.68 and 39.03 μmoles substrate/minute/mg protein, respectively. The increase in LDH activity was not significant in the 10 ppm group, but the increase in the 25 ppm group was significant at the $p<0.02$ level. No adverse effects were observed on body weight gain, liver/body weight and gross or histopathological parameters that were attributable to carbofuran treatment. Slight fatty change was observed in the livers of control as well as treated rats and was not related to the presence or dose of carbofuran in the feed.

Tobin (1970) reported observing no effects in dogs and rats fed 20 and 25 ppm carbofuran, respectively, for 2 years. The study has not been published and no other experimental data were reported in Tobin's (1970) review.

5.6. OTHER RELEVANT INFORMATION

An oral LD_{50} as low as 2 mg/kg for mice and 11 mg/kg for humans has been reported by NIOSH (1983). A principal toxic effect of the carbamates is the inhibition of cholinesterase activity.

Inhibition of acetylcholinesterase in blood or tissues by carbofuran in rats (Abdel-Aal and Helal, 1980; Borkowska and Tyburczyk, 1981) and mice (McGloin et al., 1980) following short-term exposure has been reported.

Adverse effects of carbofuran on the immune resonse in mice (Fan, 1981) and rabbits (Street and Sharma, 1975) following short-term dietary administration have been reported.

According to the ACGIH (1980), the FMC Corporation stated that occupational exposure to airborne carbofuran at concentrations approaching 0.1 mg/m^3 was without effect.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute lethality of carbofuran has been studied in many freshwater fish (Table 6-1). The 96-hour LC_{50} values for most fish species ranged from 0.147-0.872 mg/ℓ. The yellow perch, Perca flavescens, was less tolerant of carbofuran than bluegill sunfish and several species of trout (Johnson and Finley, 1980). The fathead minnow, Pimephales promelas, was the most tolerant species tested, with a 96-hour LC_{50} value of 0.872 mg carbofuran/ℓ. Furadan, which contains only 5% carbofuran, appears much less toxic than relatively pure carbofuran, but when values for three species tested are expressed on a carbofuran weight basis, toxic levels are within or slightly below the previously stated range (Hejduk and Svobodova, 1980). Carbofuran was more toxic when tested in rice paddy water under static conditions than in paddy water with intermittent flow or in tap water by static or flow testing (Brown et al., 1979). Alkaline hydrolysis to a less toxic degradation product was cited as a possible cause for this since paddy water was more acidic (pH 6.4 vs. 8.5) and agitation would tend to increase hydrolysis.

The 96-hour LC_{50} value for the estuarine sheepshead minnow, Cyprinodon variegatus, determined in a flowthrough system was 0.386 mg carbofuran/ℓ (Parrish et al., 1977; Hansen and Parrish, 1977).

6.2. CHRONIC TOXICITY

In the air-breathing catfish, Clarias batrachus, exposure to 0.5 mg carbofuran/ℓ for up to 60 days resulted in no mortality or apparent signs of toxicity (Mukhopadhyay et al., 1982). Biochemical changes as a result of carbofuran treatment included changes in enzyme activities in several tissues, serum ion changes and bioaccumulation of carbofuran and a 3-hydroxy-metabolite in the liver.

TABLE 6-1

Acute Toxicity of Carbofuran to Freshwater Fish

Species	Duration (hours)	LC_{50} (mg/ℓ)	Method	Reference
Rainbow trout, Salmo gairdneri	96	0.380	static	Johnson and Finley, 1980
Rainbow trout, S. gairdneri	48	8.5[a]	NR	Hejduk and Svobodova, 1980
Brown trout, Salmo trutta	96	0.560	static	Johnson and Finley, 1980
Lake trout, Salvelinus namaycush	96	0.164	flowthrough	Johnson and Finley, 1980
Coho salmon, Oncorhynchus kisutch	96	0.530	static	Johnson and Finley, 1980
Green sunfish, Lepomis cyanellus	72	0.16	static	Davey et al., 1976
Bluegill sunfish, Lepomis macrochirus	96	0.240	static	Johnson and Finley, 1980
Bluegill sunfish, L. macrochirus	96	0.25	static	Klaassen and Kadoum, 1979
Fathead minnow, Pimephales promelas	96	0.872	static	Johnson and Finley, 1980
Channel catfish, Ictalurus punctatus	96	0.248	static	Johnson and Finley, 1980

TABLE 6-1 (cont.)

Species	Duration (hours)	LC_{50} (mg/ℓ)	Method	Reference
Channel catfish, I. punctatus	96	0.37[b]	static	Brown et al., 1979
Channel catfish, I. punctatus	96	0.48[b]	intermittent flow	Brown et al., 1979
Yellow perch, Perca flavescens	96	0.147	static	Johnson and Finley, 1980
Carp, Cyprinus carpio	48	1.0[a]	NR	Hejduk and Svobodova, 1980
Carp, C. carpio	96	0.27	static-renewal	Verma et al., 1981b
Mosquitofish, Gambusia affinis	72	0.52[a]	static	Davey et al., 1976
Guppy, Poecilia reticulata	48	3.4[a]	NR	Hejduk and Svobodova, 1980
Freshwater singli, Saccobranchus fossilis	96	0.547	static-aerated	Verma et al., 1982
Mystus vittatus	96	0.310	static	Verma et al., 1981a
Ophiocephalus punctatus	96	0.180	static	Verma et al., 1981a

[a]Testing was done with Furadan which contained 5% carbofuran. Result expressed as mg Furadan/ℓ.

[b]Testing conducted in rice paddy water.

Larval stage carp, Cyprinus carpio, were used to determine 96-hour LC_{50} values and 60-day MATC for carbofuran (Verma et al., 1981b). Mortality was determined in the 96-hour tests and mortality and weight gain (standing crop) were determined in 60-day tests. The 96-hour LC_{50} for larval C. carpio exposed to carbofuran was 0.27 mg/ℓ while the MATC range was 0.014-0.18 mg/ℓ. These authors (Verma et al., 1981b) suggested a safe concentration of 0.0026 mg carbofuran/ℓ based on the 96-hour and 60-day tests.

Life-cycle toxicity testing of carbofuran was conducted with sheepshead minnows, Cyprinodon variegatus (Parrish et al., 1977; Hansen and Parrish, 1977). Juvenile fish were exposed to carbofuran during maturation at 0.006, 0.015, 0.023, 0.049 and 0.100 mg/ℓ in artificial seawater for ~6 weeks before spawning. Exposure continued through spawning, embryonic development and fry stages of the F_1 for a total of 19 weeks. Mortality was significantly ($p<0.05$) increased in adult fish treated at 0.049 and 0.100 mg/ℓ. Hatching success of embryos was significantly ($p<0.05$) reduced at 0.049 mg carbofuran/ℓ. Survival of fry was significantly ($p<0.05$) decreased at 0.023 and 0.049 mg/ℓ. MATC for carbofuran was reported to be 0.015-0.023 mg/ℓ based on the embryo-larval toxicity testing.

6.3. PLANT EFFECTS

Carbofuran exposure at 0.0075, 0.015 and 0.030 mg/ℓ caused dose-related growth reduction in the blue-green alga, Nostoc muscorum (Kar and Singh, 1979). Nutrient levels influenced the extent of carbofuran toxicity. Furadan (3% carbofuran) at 25 mg/ℓ enhanced the survival, growth and nitrogen fixation of N. muscorum. At concentrations of 50-1000 mg/ℓ growth was inhibited and levels of 1200 mg Furadan/ℓ were algicidal (Kar and Singh, 1978).

6.4. RESIDUE

Sangha (1971) reported that carbofuran (initial concentration not reported in the abstract) had low residual activity in the biological components of a model ecosystem, with 370 ppb found in mosquito larvae and 1200 ppb in fish (i.e., Gambusia), Klaassen and Kadoum (1979) failed to detect any carbofuran residues on any sampling day in zooplankton, black bullheads or bluegills in a pond ecosystem treated with carbofuran. Yu et al. (1974) also failed to find carbofuran residues in caterpillars, freshwater clams, freshwater crabs or frogs when 5 mg ^{14}C-carbofuran was applied to sorghum plants growing in a laboratory aquatic ecosystem.

6.5. OTHER RELEVANT INFORMATION

The metabolism of carbofuran by liver microsomal preparations of the podifield fish, Trichogaster pectoralis, was studied by Gill (1980). The two major and three minor metabolites identified were N-hydroxy methyl carbofuran, 3-hydroxy-carbofuran, 3-ketocarbofuran, carbofuran phenol and 3-keto-phenol. The metabolism of carbofuran, which appears to be primarily N-hydroxylation, required NADPH.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The American Conference of Governmental Industrial Hygienists (ACGIH, 1980) has recommended a TLV of 0.1 mg/m³ for an 8-hour TWA.

Tolerances for carbofuran residues have been established for a variety of raw agricultural commodities intended for human consumption. They range from 0.05 ppm for animal fat, meat and meat by-products to 2 ppm in potatoes and beets (40 CFR 180.254, 1982).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of carbofuran were not located in the available literature.

8. RISK ASSESSMENT

Carbofuran does not appear to have mutagenic activity, although a positive micronucleus test has been reported. No available studies to date have specifically investigated or demonstrated tumorigenicity. The only chronic data available are the 2-year dietary studies reported by Tobin (1970), in which no-effect levels of 25 ppm for the rat and 20 ppm for the dog were determined. Sufficient experimental details necessary for an evaluation of this study, however, were not reported. In deriving criteria for this compound, reliance must be also placed, therefore, on the data from subchronic studies.

Decreased survival in mice upon dietary administration of 100 ppm carbofuran for 8 months was reported by Wolfe and Esher (1980). Dietary administration of 100 ppm to rats in a 3-generation reproductive study was associated with reduced body weights and survival of weanlings (Clegg, 1979). Biochemical effects on the ventral prostate of rats have been observed in a 90-day study at dietary levels of 30 ppm (Shain et al., 1977) and increases in serum and hepatic lactic dehydrogenase, but no histopathologic effects, were observed at dietary levels of 10 and 25 ppm, administered for 180 days (Rotaru et al., 1981).

The lowest dose level that produced an effect was a single gavage application of 0.05 mg carbofuran/kg, which inhibited blood cholinesterase activity in fasted female rats and their offspring (Cambon et al., 1979). These effects were transitory, not clearly adverse, and it was speculated that the relatively high transient blood levels occurring after gavage administration to fasted rats resulted in these acute effects following this low level exposure.

Taken together, the data from these chronic and subchronic studies suggest a dietary NOAEL of 25 ppm for the rat. The few data that are available for other species do not indicate that other species would be more sensitive to this compound than are rats. Assuming that a rat's daily food consumption is equivalent to 5% of its body weight, the dosage of carbofuran resulting from a 25 ppm dietary level is estimated at 1.25 mg/kg/day. An uncertainty factor of 1000 is appropriate for calculating an ADI for humans, because the NOAEL for rats is based on an unpublished chronic study (for which no experimental details were available) and subchronic studies that were limited in scope and adequacy. Application of this uncertainty factor results in an ADI of 0.00125 mg/kg/day, or 0.088 mg/day for a 70 kg man.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal and human data that indicate that the ADI derived above may not provide sufficient protection for humans. Overt cholinergenic symptoms occurred in human subjects treated orally with a single dose of 0.25 mg/carbofuran/kg bw. Several studies in rats, however, define a dietary level of 20 ppm carbofuran, equivalent to a dosage of 1 mg/kg bw/day, as a NOEL for this species. These data indicate that rats may be substantially less sensitive to carbofuran than are humans. Since no studies of repeated treatment of humans with lower doses were available for review in the CBI Appendix, however, the data base is inadequate to define a NOAEL; therefore, no ADI can be recommended.

9. REFERENCES

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APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

These searches were conducted in May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

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